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10/774,358	02/05/2004	William Stern	P/546-279 REISSUE	8408

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,358	STERN, WILLIAM	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/11/07 & 10/12/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/11/07 & 10/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments, Remarks, IDS and Declaration filed on 09/11/07 and supplemental Remarks, Declaration and IDS filed on 10/12/07. Accordingly, claims **13-44** remain pending.

In light of the Amendments, Remarks and Declarations the rejections of claims under 112 and anticipation by Chiodini and Grebow references have been withdrawn. However the rejection of claims under obviousness is maintained and upon further consideration new grounds of rejections are deemed necessary.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 13-14, 17, 20-23, 34, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiodini et al (5,719,122).

Chiodini et al disclose pharmaceutical compositions comprising a **calcitonin** and a polyglycolysed glyceride and a method of enhancing the transmucosal absorption of calcitonin. Calcitonin may be a natural or synthetic calcitonin. Human, **salmon** and eel calcitonins are the most preferred types (see col. 2, line 50 to col. 4, line 19). The said polyglycolysed glycerides which are suitable for the said formulations include polyethylene glycol esters such as Labrasol™ and Gelucire 44/14™ (see col. 2, lines 19-34). The **nasal** formulations are typically in solution, gel, drops or **aerosol** forms (see col. 5, lines 14-16). The **pH** of the composition is suitably at a range of from 3 to 8,

preferably **3.5 to 7**. A buffering agent such as citrates, for example a mixture of citric acid and sodium citrate is employed to adjust the pH levels (see col. 6, lines 13-25). Example 19 discloses a solution formulation for nasal or buccal administration. The total amount of the citrates used in the said formulation is about 18 mM. The pH is adjusted to 6. Other ingredients may be used in the said formulations such as polyhydroxy alcohols such as propylene glycol; excipients such as parabens and benzyl alcohol, agents for adjusting viscosity, agents for adjusting tonicity, etc (see col. 5, lines 52-65).

Chiodini et al does not exemplify a formulation comprising calcitonin, a citrates in the amount of 10-25 wherein the pH is between 3.5 and 3.9, however Chiodidni et al discloses a solution comprising calcitonin and citrates for nasal administration and it teaches that suitable pH levels are between 3.5 and 7. Thus one of ordinary skill in the art would have been able to adjust the pH to any pH levels from 3.5 and 7. In other words, claims would have been obvious because the technique for improving a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

Claims 13-14, 17, 20-23, 34, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grebow et al (5,026,825).

Grebow et al teaches an **intranasal** formulation comprising **calcitonin** and excipients. The **salmon** and chicken calcitonins have a potency of about 4,000 to 6,000

MCR U/mg peptide (col. 3, lines 4-15). The said formulations may be administered across the **nasal membranes** as a spray, nose drop or aerosol (col. 11, lines 15-21).

Grebow also discloses that the nasal spray solutions are especially preferred with water or in a buffer at a **pH of between 3.0 and 8.0** using a buffer system including a mixture of sodium citrate and citric acid in the range of **0.01 M to 0.5 M**. This concentration range was found effective to **provide stability** of the dissolved calcitonin in the diluent base or vehicle (col. 11, lines 35-47). Furthermore the formulations are said to have been made in 0.2M buffer at a pH value of 4.1 (col. 14, lines 34-35). The preparations may also comprise other additives including stabilizers, tonicity adjusters, viscosity builders, preservatives and the like (col. 11, lines 48-52). The said additives include methyl paraben, propyl paraben, phenethyl alcohol, etc. Grebow discloses certain suitable concentration ranges of the said additives in the table of column 12.

Grebow et al's ranges on pH levels and concentration of citrates for the nasal formulations comprising calcitonin are broader than that required by the instant claims, however, the claimed ranges are disclosed within the broad range and they meet the narrower ranges of the claims. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have chosen a suitable amount of citrates to produce a formulation with a more acidic pH (lower pH levels) with a reasonable expectation of successfully preparing a formulation that is efficient and stable. In other words, the claim would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If

this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Claim 15-16, 18-19, 24-33, 35-39 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grebow et al (5,026,825) as applied to claims 13-14, 17, 20-23, 34, 40-42 above, and further in view of Azria et al (5,733,569).

Grebow et al, discussed above, lacks specific disclosure on the osmolality and viscosity of the formulations.

Azria et al discloses galenic compositions comprising calcitonin for nasal administration. Azria discloses that preferred **pH** levels for a nasal formulation is from 3 to 5 or most preferably from **3.5 to 4.5**. The formulation also should have an appropriate isotonicity and viscosity. Preferably the osmotic pressure is from **about 260 to about 380 mOsm/l** and the desired viscosity is from 2 to about $40x10^{-3}$ Pa.S or more preferably less than $2x10^{-3}$ Pa.s (see col. 4, lines 13-28).

It would have been obvious to one of ordinary skill in the art given the nasal solution formulations of Grebow et al to have looked in the art for suitable osmolality and viscosity for intranasal administration as taught by Azria et al, for ultimate effectiveness and safety. It is clearly stated by Azria et al and other prior art references and well known in the art that for delivery to sensitive mucosa such as nasal, eye, ear, etc, specific ranges in osmolality, isotonicity and viscosity are required. Thus one of

ordinary skill in the art would have been motivated to have made certain the required properties are present in a formulation for nasal administration. In other words the combination of references provides sufficient information to one of ordinary skill in the art to make and use the invention as claimed.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ventra (EP 0418697).

Ventra teaches pharmaceutical compositions containing calcitonin. It is also disclosed that the known formulations are not satisfactory in at least one of the following aspects: **bioavailability, stability**, tolerability and safety (page 2). The stability and bioavailability tests show that the formulations as prepared are more stable and have better bioavailability (see page 3). Examples 1-4 disclose formulations that comprise calcitonin and about 37 mM of citrates. The pH is maintained at a level of 4.0 $\pm$ 0.3 (see pages 4-5).

Although Ventra does not specifically disclose a method of improving stability or bioavailability of a calcitonin formulation comprising adding citrates, it does disclose that the formulations as prepared are more stable and have improved bioavailability. Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the disclosure of Ventra and conclude that adding citrates to a calcitonin formulation would have improved stability and

bioavailability of the said calcitonin formulation. Furthermore, the claims would have been obvious to one of ordinary skill in the art because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Response to Arguments

Applicant's arguments with respect to claims 13-44 have been considered but are moot in view of the new ground(s) of rejection. However, Applicant's arguments and Dr. Stern's Declarations would be responded to here.

Applicant argues and Dr. Stern states in the Declaration of 09/11/07, that when Grebow reference discloses the term "stability" in column 11, it is in reference to the buffer system or a short-term stability and not the shelf stability, as disclosed in Table 3 of the present specification. This is not persuasive because 1) most instant claims (except for claim 22 and its depending claims) are drawn to a formulation, a method of administration or a method of improving bioavailability. The issue of stability is not a limitation of any of these claims. Thus Applicant's arguments regarding stability, whether shelf stability or buffer stability, are not commensurate with the scope of instant claims. 2) For claim 22 and its dependent claims, a method of improving stability of a liquid pharmaceutical composition, the scope of claim requires an improvement of stability of the formulation and does not distinguish between buffer stability or shelf stability. 3) Table 3 shows best stability for a formulation comprising 10 mM of citrate

while 50 mM citrate has lower stability. Thus Applicant's arguments that improved stability has been shown for a formulation comprising from 10-50 mM has not been shown and Grewbow's formulations meet this limitation. 4) Table 3 shows data collected at 50°C. It would have been expected that formulations are kept at room temperatures, if not lower. The instant claims do not recite a temperature limitation and it is considered that Grebow's formulations are kept at room temperature. Thus arguments regarding data shown in Table 3 are not commensurate with scope of claims.

It is further noticed that claims 22 and 23 both recite improved stability and bioavailability (respectively) at concentration levels of 10-50 mM citrate. While Table 1 shows best degree of bioavailability at **100 mM** citrate, Table 3 shows best level of stability at **10 mM** citrate. Also claims recite a "bioavailability enhancing agent selected from citric acid or its salts", but Applicant is basically arguing improved stability. There does not appear to be any reasons for the said inconsistencies in the specification or arguments. It is the Examiner's position that Applicant's arguments or Declarations do not distinguish the instant claims from teachings of prior art of record and no claim is considered allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mina Haghighatian
Patent Examiner
November 06, 2007